Prevalence of Delayed Gastric Emptying in Diabetic Patients and Relationship to Dyspeptic Symptoms

A prospective study in unselected diabetic patients

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OBJECTIVE — Data on the prevalence of abnormal gastric emptying in diabetic patients are still lacking. The relation between gastric emptying and dyspeptic symptoms assessed during gastric emptying measurement has not yet been investigated. The aim was to investigate the prevalence of delayed gastric emptying in a large cohort of unselected diabetic patients and to investigate the relation between gastric emptying and gastrointestinal sensations experienced in the 2 weeks before and during the test meal, prospectively.

RESEARCH DESIGN AND METHODS — Gastric emptying was evaluated in 186 patients (106 with type 1 diabetes, mean duration of diabetes 11.6 ± 11.3 years) using 100 mg 13C-enriched octanoic acid added to a solid meal.

RESULTS — Gastric emptying was significantly slower in the diabetic subjects than in the healthy volunteers (T90: 99.5 ± 33.4 vs. 76.8 ± 21.4 min, P < 0.003; Ret120 min: 30.6 ± 17.2 vs. 20.4 ± 9.7%, P < 0.006). Delayed gastric emptying was observed in 51 (28%) diabetic subjects. The sensations experienced in the 2 weeks before the test were weakly correlated with the sensation scored during the gastric emptying test. Sensations assessed during the gastric emptying test did predict gastric emptying to some extent (r = 0.46, P < 0.0001), whereas sensations experienced in the previous 2 weeks did not.

CONCLUSIONS — This prospective study shows that delayed gastric emptying can be observed in 28% of unselected patients with diabetes. Upper gastrointestinal sensations scored during the gastric emptying tests do predict the rate of gastric emptying to some extent and sensation experienced during daily life does not.

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The prevalence of delayed gastric emptying in patients with diabetes has been subject to debate for several decades. Cross-sectional studies using scintigraphic techniques to measure gastric emptying have shown delayed gastric emptying in patients with diabetes varying from 30 to 60% (1–11). However, there are several important limitations to these studies. First, the vast majority of these studies have been performed in small numbers of patients or in selected patients, which may account for the high percentage of patients showing delayed gastric emptying in some of these studies. Second, none of these studies has been performed during relative euglycemic conditions, whereas recent studies have provided evidence that hyperglycemia has a substantial effect on the rate of gastric emptying (12,13). After taking the aforementioned into account, the prevalence of delayed gastric emptying in diabetic patients who are not selected for gastrointestinal symptoms has yet to be determined.

Previous studies have reported a weak association between gastric emptying and upper gastrointestinal symptoms experienced by patients in the period preceding the gastric emptying test, with the exception of the study performed by Jones et al. (10). They studied a large cohort of diabetic subjects over a period >10 years and reported that abdominal bloating and fullness were associated with the gastric emptying rate.

To date no studies have investigated the relation between gastrointestinal sensations assessed during the gastric emptying test and gastrointestinal sensations experienced in daily life. Moreover, no studies have investigated the predictive value of upper gastrointestinal sensations for the rate of gastric emptying after a similar standardized stimulus, in this case the same meal.

As in our study, several studies (14–19) have used the 13C-octanoic breath test to evaluate gastric emptying in healthy humans and in a number of diseases, including diabetes. The advantages of this test over the gold standard, the radioisotope technique, are the relatively low costs and the lack of radiation involved. Therefore, the 13C-octanoic breath test has become a valuable and reliable tool to investigate gastric emptying in large cohorts of patients (19).
Table 1—Demographic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of diabetes</td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>106 (57)</td>
</tr>
<tr>
<td>Type 2</td>
<td>80 (43)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>11.6 ± 11.3; range 1–54</td>
</tr>
<tr>
<td>Insulin</td>
<td>155 (83)</td>
</tr>
<tr>
<td>Oral hypoglycemic drugs</td>
<td>19 (10)</td>
</tr>
<tr>
<td>Insulin and oral hypoglycemic drugs</td>
<td>12 (7)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
</tr>
<tr>
<td>5.1–6.5</td>
<td>39 (21)</td>
</tr>
<tr>
<td>7.1–9.0</td>
<td>147 (79)</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>35 (19)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>36 (19)</td>
</tr>
</tbody>
</table>

Data are n (%) or means ± SD.

The purpose of our study was to investigate the prevalence of delayed gastric emptying in a large cohort of diabetic patients not selected on the basis of upper gastrointestinal symptoms, prospectively. Furthermore, we aimed to investigate the relation between upper gastrointestinal sensations experienced by the patients in the 2 weeks before and during the gastric emptying test and their predictive value for the rate of gastric emptying.

RESEARCH DESIGN AND METHODS—Over 12 months, patients with diabetes attending the outpatient clinic for internal medicine (Departments of Internal Medicine at the University Medical Center, Utrecht, and at Eemland Hospital, Amersfoort) were invited to participate in the study. Gastric emptying and gastrointestinal sensations were assessed in 186 diabetic patients (70 women, aged 46 ± 11 years, weight 81 ± 15 kg, and BMI 26.5 ± 5.3 kg/m²). Exclusion criteria included the following: any medication known to influence gastrointestinal motility with the exception of insulin and oral hypoglycemic drugs, pregnancy, a history of peptic ulcer disease, a history of gastrointestinal surgery other than cholecystectomy and appendectomy, and evidence of clinically significant cardiovascular, pulmonary, renal, and hepatic diseases. Demographic characteristics of the patients are presented in Table 1.

Gastric emptying studies were also performed in 54 healthy volunteers (36 women, aged 39 ± 15 years, weight 73 ± 12 kg, BMI 24.2 ± 2.8 kg/m²) who were taking no medication and without evidence of gastrointestinal, metabolic, and pulmonary diseases. Written informed consent was obtained from all subjects, and the study was approved by the ethics committee of the University Medical Center, Utrecht, and the Eemland Hospital, Amersfoort.

Study procedure
Screening for study participation was performed at least 3 days before the study by one investigator (M.S.). Patients were given instruction about their insulin dosing the evening before and the day of the study. Oral hypoglycemic drugs were taken at the usual time. At 8:00 A.M., fasting glucose concentrations were measured and the appropriate dose of insulin was self-administered by the insulin-dependent diabetic subjects. Gastrointestinal sensations experienced by the patients during the previous 2 weeks were assessed using a standard questionnaire (3). The gastric emptying tests started when the blood glucose concentration was <10 mmol/l or 60 min had elapsed after the first blood sample for the measurement of blood glucose concentration. Fasting breath samples were obtained, and gastrointestinal sensations were scored using visual analog scales before meal ingestion. After meal ingestion, breath samples and gastrointestinal sensations were obtained every 15 min for 4 h.

Assessment of gastrointestinal sensations
The gastrointestinal sensations (fullness, nausea, vomiting, and upper abdominal pain or discomfort) were assessed before meal ingestion by one investigator (E.D.) according to the following scheme: 0 = none, 1 = mild (symptoms could be ignored if patient did not think about them), 2 = moderate (symptom could not be ignored but did not influence daily activities), and 3 = severe (symptoms influenced daily activities) (3). Hunger was scored using a 3-point scale ranging from not hungry at all to very hungry.

Directly before and during the gastric emptying test, gastrointestinal sensations induced by the test meal were assessed at 15-min intervals by the same investigator (E.D.) using a visual analog scale. Symptoms that were scored included fullness, nausea, vomiting, and upper abdominal pain or discomfort. In addition, satiety-related sensations were scored: hunger, wish to eat, and prospective feeding intentions (20, 21).

Measurement of gastric emptying
The test meal consisted of two eggs, and one egg yolk was dosed with 100 mg 13C-octanoic acid (Campro Scientific, Veenendaal, the Netherlands) (14–17). The egg yolk containing 13C-octanoic acid and the egg white with the second egg yolk were baked separately. The eggs were placed on a slice of whole wheat bread and given with 200 ml water (total caloric content, 286 kcal). The meal was consumed within 10 min. Breath samples were obtained before the meal and after at 15-min intervals for up to 4 h. Each breath sample was collected in a 10-ml glass vacutainer using a straw to blow into the bottom of the tube. The 13CO2 breath content was measured by isotope ratio mass spectrometry (Breathmat; Finnegan, Bremen, Germany) (14–17).

Data analysis of breath test
The Pee-Dee Belemnite standard was used for calibration. CO2 production was corrected for age, sex, height, and weight using the algorithms of Schofield (22). Mathematical analysis of the 13C values in the breath samples was performed using a generalized linear regression model adopted from Lee et al. (18) and Viramontes et al. (19).

Selection of the time points to predict...
Gastric emptying and dyspeptic symptoms

Gastric emptying was based on the results of a study (23) in which both scintigraphy and breath test measured gastric emptying. Additional gastric emptying studies in healthy volunteers (n = 24) and in patients with diabetes (n = 40) resulted in a correlation coefficient of 0.82 (P < 0.0001) for gastric emptying half-time (T50) and 0.79 (P < 0.0001) for the percentage of the meal retained at 120 min (Ret120 min). The first step was to model the 13C excretion curves using a nonlinear curve-fitting procedure using the formula t = m · k · b · e^(-kt) · (1 - e^(-kt) · b - 1), in which m, k, and b are fitting parameters. The generalized linear regression analysis after the initial curve-fitting procedure selected seven time points for the prediction of scintigraphic gastric emptying half-time and eight time points for the prediction of the percentage of the meal retained in the stomach at 120 min. Selected time points were: T50; t = 15, 30, 150, 180, 210, and 225 min and Ret120 min; t = 15, 30, 105, 120, 180, 193, 210, and 225 min.

Statistical analysis
Multiple regression analysis and repeated measurements ANOVA were used to analyze sensation and gastric emptying variables. Pearson correlation coefficient was used to study the association between variables. Data are shown as mean ± SD, unless stated otherwise. P < 0.05 was considered significant in all analyses. Gastric emptying was classified as abnormal when the rate of gastric emptying was outside the range obtained from the 54 healthy volunteers (mean ± 2 SD).

RESULTS — Gastric emptying data obtained from two diabetic patients were excluded from further analysis because of technical failure of the isotope ratio mass spectrometer. Data obtained from four diabetic patients could not be analyzed using the mathematical model due to inability to fit the curves or missing data from the selected breath samples. The remaining breath samples obtained from 182 patients were used for further statistical analysis.

No patients dropped out because of incomplete ingestion of the meal or vomiting after the meal. The mean fasting blood glucose concentration was 14.0 ± 3.5 mmol/l. After insulin administration, the mean glucose concentrations for the total group (insulin + noninsulin users) was 9.4 ± 3.2 mmol/l.

Gastric emptying in patients with diabetes
Gastric emptying was significantly slower in the patients with diabetes than in the healthy volunteers (T50: 95.9 ± 35.4 vs. 76.8 ± 21.4 min, P < 0.003; Ret120 min: 30.6 ± 17.2 vs. 20.4 ± 9.7%, P < 0.006). The Ret120 min value was strongly correlated with T50 (r = 0.81, P < 0.0001). T50 for the meal was prolonged in 40 (22%) of the patients (Fig. 1A). The Ret120 min value was above the upper limit of normal in 51 (28%) of the patients (Fig. 1B).

Gastric emptying was slower in diabetic women than in diabetic men (T50: 106.1 ± 39.4 vs. 95.2 ± 32.0 min, P < 0.04; Ret120 min: 35.1 ± 18.2 vs. 27.7 ± 16.3%, P < 0.005). The rate of gastric emptying was not related to age (r = 0.06, NS), BMI (r = 0.035, NS), duration of diabetes (r = 0.02, NS), or fasting glucose concentration (r = 0.043, NS). The type of diabetes did not affect the rate of gastric emptying (T50: 102.4 ± 34.8 vs. 91.5 ± 26.4 min, P = 0.3, for type 1 and type 2 diabetic subjects, respectively). T50 in patients with HbA1c < 6.5% was comparable with the T50 in patients with HbA1c > 6.5% (93.1 ± 35.2 vs. 99.6 ± 38.2 min, P = 0.23, for type 1 and type 2 diabetic subjects, respectively).

Moreover, no differences in gastric emptying rate were observed in patients with and without complications, such as peripheral neuropathy (T50: 95.9 ± 37.9 vs. 100.3 ± 34.8 min, respectively), retinopathy (T50: 97.2 ± 33.5 vs. 97.2 ± 35.6 min), or nephropathy (T50: 99.8 ± 37.6 vs. 99.4 ± 35.0 min).

Gastrointestinal sensations in patients with diabetes
Gastric emptying was significantly slower, as assessed by Ret120 min, in patients with complaints of fullness (P < 0.003) and upper abdominal pain (P < 0.007) experienced in the previous 2 weeks. In addition, patients who reported to be less hungry showed slower gastric emptying (P < 0.018). In contrast, sensations of nausea and vomiting were not related to gastric emptying. However, gastric emptying was slower in patients with more complaints of fullness and upper abdominal pain and who felt less hungry; these sensations did not predict gastric emptying (r = 0.18, NS).

The sensations experienced by the diabetic patients in the 2 weeks prior to the study correlated only weakly with the sensation scored during the gastric emptying test (Tables 2 and 3). The relation between each individual sensation was of the same magnitude as the relation between different sensations.

Patients with a retention >40% at 120 min showed significantly higher fullness scores (VAS 0–100) than patients with 0–40% of the meal retained in the stomach (P < 0.001) (Fig. 2). Fullness- and satiation-related sensations were significantly, albeit weakly, correlated with gastric emptying. In contrast, nausea and abdominal pain were not correlated with gastric emptying at any time point (Fig. 3).

The sensation scores obtained during the gastric emptying test could be reduced to two noncorrelated factors (factor 1: fullness, nausea, vomiting, and upper abdominal pain or discomfort; factor 2: hunger, wish to eat, and prospective feeding intentions). Multiple regression with forward selection selected four time points (45, 120, 180, and 225 min) when dyspeptic symptoms were scored (factor 1) and one time point (45 min) when satiation-related sensations were scored to predict T50 and Ret120 min (r = 0.46, P < 0.0001 and r = 0.43, P < 0.0001, respectively).

CONCLUSIONS — This prospective study performed in a large unselected cohort of patients with diabetes shows that the prevalence of delayed gastric emptying is 28% in relatively well-regulated patients with diabetes. Delayed gastric emptying was related to sex but not duration of diabetes, glycemic control, or non-gastrointestinal complications.

Patients with delayed gastric emptying reported more complaints of fullness and abdominal pain and felt less hungry in the 2 weeks before the gastric emptying test. However, multiple regression analysis showed that these symptoms did not predict the rate of gastric emptying. In contrast, sensations assessed during the gastric emptying test did predict gastric emptying to some extent. Especially, fullness- and satiation-related sensations could be used as predictors of the rate of gastric emptying.

Horowitz et al. (3) studied the largest
cohort of patients with diabetes over a decade ago. They reported delayed gastric emptying in about 45% of the patients. In their cohort, Horowitz et al. found that glycemic control was poor in >50% of patients. In addition, blood glucose concentrations were >15 mmol/l in 55% of the patients during the gastric emptying test. It is therefore difficult, if not impossible, to extrapolate these data to today's diabetic population.

In the present study, patients were recruited from outpatient clinics for diabetes without selection on the basis of upper gastrointestinal sensations or poor glycemic control. The gastric emptying tests were started as soon as the blood glucose levels were within or close to the euglycemic range in the large majority of the patients. Both factors are likely responsible for the lower incidence of delayed gastric emptying observed in the present study compared with previous studies (1–11).

The rate of gastric emptying in our cohort of patients with diabetes was related to sex but not duration of diabetes, which is in line with the observations by Jones et al. (10). Recently, Bytzer et al. (24) showed that dyspeptic symptoms are related to poor glycemic control. In the present study, however, we observed no relation between poor glycemic control and delayed gastric emptying, suggesting that the relation between dyspeptic symp-

Table 3—Relation between the sensations experienced by the patients in the 2 weeks before the gastric emptying test and during the gastric emptying test

<table>
<thead>
<tr>
<th>Sensations</th>
<th>Fullness</th>
<th>Nausea</th>
<th>Pain or discomfort</th>
<th>Hunger</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fullness</td>
<td>0.33</td>
<td>0.28</td>
<td>0.32</td>
<td>−0.26</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.25</td>
<td>0.30</td>
<td>0.29</td>
<td>−0.25</td>
</tr>
<tr>
<td>Pain or discomfort</td>
<td>0.32</td>
<td>0.27</td>
<td>0.21</td>
<td>−0.22</td>
</tr>
<tr>
<td>Hunger</td>
<td>−0.11</td>
<td>−0.21</td>
<td>−0.22</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Figure 1—Distribution of $T_{50}$ (A) and Ret$_{120\text{ min}}$ (B). A $T_{50} > 120\text{ min}$ (mean ± 2 SD) and Ret$_{120\text{ min}} > 40\%$ are outside the normal range.
and glycemic control observed by Bytzer et al. is determined by factors (e.g., altered visceral perception and impaired gastric accommodation) other than the rate of gastric emptying. Also, it cannot be excluded that the number of subjects studied was too small to detect a relationship between poor glycemic control and delayed gastric emptying.

The delay in gastric emptying observed in our studies is most likely due to reversible or irreversible autonomic dysfunction at the level of the extrinsic nervous system and/or the myenteric plexus (25–27). Without doubt, the actual blood glucose concentration plays an important role in reversible autonomic dysfunction because it has been shown that blood glucose concentration affects vagal tone and blunt gastrocolonic reflexes (28,29).

In the present study, the glucose concentrations were within or close to the euglycemic range at the time the meal was ingested in the majority of patients. In addition, the blood glucose concentrations in the diabetic patients were not related to the rate of gastric emptying (r = 0.043). Therefore, it is unlikely that the actual blood glucose concentration affected the outcome of the present study to a large extent.

Several studies (2–4,10,30,31) have reported a poor relation between upper gastrointestinal symptoms experienced in daily life and gastric emptying in diabetes. These observations were confirmed in the present study. Although gastric emptying was slower in patients with a higher score for fullness and upper abdominal pain, these sensations did not predict delayed gastric emptying and are therefore of little use to the clinician as a guidance for therapy.

The sensations experienced by the patients in the 2 weeks before the gastric emptying study were weakly related to the sensation observed after ingestion of the standard meal. These findings are in line with observations by Whitehead et al. (32) in patients with irritable bowel syndrome. They investigated the relation between pain reported by irritable bowel syndrome patients in the 2 weeks before the study and pain experienced during rectal distension and reported a correlation between the two that was comparable with the correlations observed in this study. At first sight this low association may be surprising. However, several factors should be taken into account. First, a recall bias may play a role in the sensations assessed by the questionnaire, evaluating symptoms experienced in the 2 weeks before the gastric emptying study.
weeks before the gastric emptying test. Second, different stimuli, in this case different types of meals, may give rise to different sensations or different intensity of sensations. Third, visceral sensitivity is influenced by actual blood glucose concentrations. Sensations may be induced by a meal during hyperglycemia that are not experienced by the subject during euglycemia (33,34).

In contrast to the sensations experienced in the previous 2 weeks, multiple regression analysis of the sensations induced by the standard meal predict gastric emptying to some extent ($r = 0.46$, $P < 0.0001$). Although the correlation at each time point was relatively weak, assessing the sensations over time increased its value as a predictor of the gastric emptying rate. Furthermore, our results indicate that satiation-related sensations should be taken into account and that these are a better indicator of the gastric emptying rate than the symptoms of nausea and upper abdominal pain or discomfort.

The fact that sensations are not invariably related to the gastric emptying rate has been well established in previous studies. The pathophysiological mechanisms that have been shown to be of importance apart from delayed gastric emptying are impaired accommodation of the stomach and increased visceral sensitivity and hyperglycemia (33–36).

In conclusion, this cohort study shows that delayed gastric emptying is observed in about 28% of unselected patients with diabetes. Delayed gastric emptying was associated with sex but not duration of diabetes, glycemic control, or nongastrointestinal complications. In contrast to symptoms experienced by the patients during daily life, sensations induced by the test meal predicted the rate of gastric emptying to some extent.

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References